



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/335	A1	(11) International Publication Number: WO 00/03705 (43) International Publication Date: 27 January 2000 (27.01.00)
(21) International Application Number: PCT/US99/13275 (22) International Filing Date: 15 June 1999 (15.06.99) (30) Priority Data: 60/092,762 14 July 1998 (14.07.98) US (71) Applicant: ALCON LABORATORIES, INC. [US/US]; R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (72) Inventors: YANNI, John, M.; 2821 Donnybrook Drive, Burleson, TX 76028 (US). GAMACHE, Daniel, A.; 5610 Hunterwood Lane, Arlington, TX 76017 (US). WEIMER, Lori, K.; 2206 Diamond Point Drive, Arlington, TX 76017 (US). (74) Agents: RYAN, Patrick, M. et al.; R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		(81) Designated States: AU, BR, CA, CN, JP, KR, MX, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: USE OF 11-(3-DIMETHYLAMINOPROPYLIDENE)-6,11-DIHYDRODIBENZ[B,E]OXEPIN-2-ACETIC ACID FOR THE MANUFACTURE OF A MEDICAMENT FOR TREATING NON-ALLERGIC OPHTHALMIC INFLAMMATORY DISORDERS AND FOR THE PREVENTION OF OCULAR NEOVASCULARIZATION (57) Abstract Ophthalmic formulations containing as an active ingredient 11-(3-dimethylaminopropylidene) -6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof are useful for inhibiting cytokine release (e.g., IL-6 and IL-8) from human ocular cells. Such formulations can be used to treat or prevent ocular neovascularization and non-allergic inflammatory disorders such as dry-eye, keratitis, blepharitis, uveitis and inflammation related to infection.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**USE OF 11-(3-DIMETHYLAMINOPROPYLIDENE)-6,11-DIHYDRODIBENZ[B,E]OXEPIN-2-ACETIC ACID
FOR THE MANUFACTURE OF A MEDICAMENT FOR TREATING NON-ALLERGIC OPHTHALMIC
INFLAMMATORY DISORDERS AND FOR THE PREVENTION OF OCULAR NEOVASCULARIZATION**

5 BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to ophthalmic pharmaceutical
10 formulations. More particularly, the present invention relates to therapeutic
and prophylactic use of 11-(3-dimethylamino-propylidene)-6,11-
dihydrodibenz[b,e]oxepin-2-acetic acid for treating and/or preventing cytokine
release from human ocular cells and resulting ocular neovascularization or
non-allergic inflammatory conditions.

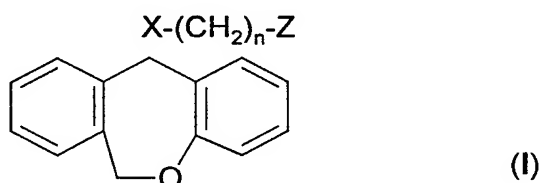
15

Description of the Related Art

As taught in U.S. Patent Nos. 4,871,865 and 4,923,892, both assigned
to Burroughs Wellcome Co. ("the Burroughs Wellcome Patents"), certain
20 carboxylic acid derivatives of doxepin, including 11-(3-
dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2-carboxylic acid
and 11-(3-dimethylamino-propylidene)-6,11-dihydrodibenz[b,e]oxepine-2(E)-
acrylic acid, have antihistaminic and antiasthmatic activity. These two patents
classify the carboxylic acid derivatives of doxepin as mast cell stabilizers with
25 antihistaminic action because they are believed to inhibit the release of
autacoids (i.e., histamine, serotonin, and the like) from mast cells and to
inhibit directly histamine's effects on target tissues. The Burroughs Wellcome
Patents teach various pharmaceutical formulations containing the carboxylic
acid derivatives of doxepin; Example 8 (I) in both of the patents discloses an
30 ophthalmic solution formulation.

U.S. Patent 5,116,863, assigned to Kyowa Hakko Kogyo Co., Ltd.,
("the Kyowa patent"), teaches that acetic acid derivatives of doxepin,

including Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, have anti-allergic and anti-inflammatory activity. The anti-inflammatory activity is attributable to prostaglandin biosynthesis inhibiting activity (see Col. 28, lines 51-57). The doxepin derivatives disclosed by the
5 Kyowa patent are represented by Compound (I):



Compounds where X represents =N-, =CH- or -CH₂- are described as having strong antiallergic activity, whereas compounds where X represents =N- are described as having strong antiinflammatory activity (see Col. 24, lines 20 –
15 57). Thus, for anti-inflammatory applications, the Kyowa patent suggests doxepin derivatives of Compound (I) where X is =N-.

The Kyowa patent demonstrates anti-allergic activity and anti-inflammatory activity in Wistar male rats. Medicament forms taught by the
20 Kyowa patent for the acetic acid derivatives of doxepin include a wide range of acceptable carriers; however, only oral and injection administration forms are mentioned. In the treatment of allergic eye disease, such as allergic conjunctivitis, such administration methods require large doses of medicine.

25 U.S. Patent No. 5,641,805 discloses topical ophthalmic formulations containing 11-(3-dimethylamino-propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for treating allergic eye diseases.

Summary of the Invention

The present invention provides a method for treating or preventing ophthalmic neovascularization and non-allergic inflammatory disorders involving cytokine release from human ocular cells. The method comprises
5 inhibiting cytokine release from human ocular cells by administering to the eye an ophthalmic formulation which contains a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (referred to as "Compound A" hereinafter) or a pharmaceutically
10 acceptable salt thereof. The formulation may contain the *cis* isomer of Compound A (Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), the *trans* isomer of Compound A (E-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), or a combination of both the *cis* and the *trans* isomers of Compound A. Unless
15 specified otherwise, "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" or "Compound A" means the *cis* isomer, the *trans* isomer or a mixture of both. "*Cis* isomer" means the *cis* isomer substantially free of the *trans* isomer; "*trans* isomer" means the *trans* isomer substantially free of the *cis* isomer. One isomer is "substantially free" of the other isomer if
20 less than about two percent of the unwanted isomer is present.

Detailed Description of the Invention

Compound A is a known compound and both the *cis* and the *trans*
25 isomers of Compound A can be obtained by the methods disclosed in U.S. Patent No. 5,116,863, the entire contents of which are hereby incorporated by reference in the present specification.

Examples of the pharmaceutically acceptable salts of Compound A
30 include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, fumarate, tartrate and citrate; alkali metal salts such as sodium salt and potassium salt; alkaline

earth metal salts such as magnesium salt and calcium salt; metal salts such as aluminum salt and zinc salt; and organic amine addition salts such as triethylamine addition salt (also known as tromethamine), morpholine addition salt and piperidine addition salt.

5

Compound A may be administered to the eye in a variety of ways. The most preferred way is by means of conventional topical ophthalmic formulations, such as solutions, suspensions or gels. Alternatively, Compound A may be administered to the eye via injection or implant.

10 Depending upon the type of formulation, conventional ingredients will be combined with Compound A. The preferred formulation for topical ophthalmic administration of Compound A is a solution administered as eye drops. The preferred form of Compound A in the ophthalmic formulations of the present invention is the *cis* isomer. A general method of preparing an eye drop
15 formulation of the present invention is described below as a nonlimiting example.

Compound A and an isotonic agent are added to sterilized purified water, and if required, a preservative, a buffering agent, a stabilizer, a viscous
20 vehicle and the like are added to the solution and dissolved therein. The concentration of Compound A is 0.0001 to 5 w/v %, preferably 0.0001 to 0.001 w/v %, and most preferably about 0.0005 w/v %, based on the sterilized purified water. After dissolution, the pH is adjusted with a pH controller to be within a range suitable for use as an ophthalmic medicine,
25 preferably within the range of 4.5 to 8.

Sodium chloride, glycerin, mannitol or the like may be used as the isotonic agent; p-hydroxybenzoic acid ester, benzalkonium chloride or the like as the preservative; sodium hydrogenphosphate, sodium
30 dihydrogenphosphate, boric acid or the like as the buffering agent; sodium edetate or the like as the stabilizer; polyvinyl alcohol, polyvinyl pyrrolidone,

polyacrylic acid or the like as the viscous vehicle; and sodium hydroxide, hydrochloric acid or the like as the pH controller.

5 If required, other ophthalmic drugs such as epinephrine, naphazoline hydrochloride, berberine chloride, sodium azulenesulfonate, lysozyme chloride, glycyrrhizate and the like may be added.

10 The eye drops produced by the above method typically need only be applied to the eyes a few times a day in an amount of one to several drops at a time, though in more severe cases the drops may be applied several times a day. A typical drop is about 30 μ l.

15 According to the method of the present invention, ophthalmic formulations containing Compound A are used to inhibit pro-inflammatory cytokine secretion from human ocular cells, such as human conjunctival epithelial cells. This type of cytokine secretion (e.g., IL-6 and IL-8) can stimulate ocular neovascularization (see, for example, Yoshida et al., IOVS, 39:1097 (1998)) and other non-allergic inflammatory conditions, such as dry eye, keratitis, blepharitis, uveitis and inflammation related to infection, for
20 example.

Certain embodiments of the invention are illustrated in the following examples.

Example 1: Preferred Topical Ophthalmic Solution Formulation

	<u>Ingredient</u>	<u>Concentration (W/V%)</u>
5	Compound A•HCl	0.111*
	Dibasic Sodium Phosphate (Anhydrous), USP	0.5
10	Sodium Chloride, USP	0.65
	Benzalkonium Chloride	0.01
15	Sodium Hydroxide, NF 7.0	q.s. pH =
	Hydrochloric Acid, NF 7.0	q.s. pH =
20	Purified Water	q.s. 100

* 0.111% Compound A•HCl is equivalent to 0.1% Compound A

25 Example 2: Topical Ophthalmic Gel Formulation

	<u>Ingredient</u>	<u>Concentration (W/V%)</u>
30	Compound A•HCl	0.11*
	Carbopol 974 P	0.8
	Disodium EDTA	0.01
35	Polysorbate 80	0.05
	Benzalkonium Chloride, Solution	0.01+5 xs
40	Sodium Hydroxide	q.s. pH 7.2
	Hydrochloric acid	q.s. pH 7.2
	Water for Injection	q.s. 100

* 0.11% Compound A•HCl is equivalent to 0.1% Compound A

Example 3: Inhibition of Cytokine Release

A. Human Conjunctival Epithelial Cell (HCE) Cultures.

Methods detailing the preparation of primary epithelial cell cultures and cytokine release studies using these cells have been described. See
5 cytokine release studies using these cells have been described. See Gamache, et al., "Secretion of proinflammatory cytokines by human conjunctival epithelial cells," *Ocul Immunol Inflamm.*, 5:117-128 (1997). Briefly, cultures of human conjunctival epithelial cells were initiated from donor tissues obtained within eight hours post mortem by various eye banks.
10 The tissues were enzymatically digested overnight. Epithelial cells were gently scraped from the tissue surface, dissociated into a single cell suspension, and cultured in keratinocyte growth medium (Clonetics®, San Diego, CA). Cells were used only through passage 6. Cultures were maintained in a preconfluent state to prevent differentiation. Cells were
15 identified as epithelial by positive keratin staining.

B. Cytokine Assays.

Several compounds with histamine H₁ antagonist activity were evaluated for their ability to inhibit secretion of cytokines (IL-6 and IL-8) from cultured
20 human conjunctival epithelial cells in response to histamine stimulation. Cells were plated at 2×10^4 cells/well and cultured overnight at 5% CO₂/37°C. The following day, fresh medium containing test compound was added directly to wells and the cells were incubated for 30 minutes prior to 24-hour stimulation with histamine (30 μM). Three separate culture wells were used for each
25 treatment group. At harvest, supernatants were collected, centrifuged at 200 x g, and stored at -20°C. Samples were analyzed for IL-6 and IL-8 by ELISA (R&D Systems, Minneapolis, MN) as directed by the manufacturer. The sensitivities of each ELISA are as follows: IL-6 0.7 pg/ml and IL-8 3.0 pg/ml.

C. Data Analysis

The antagonist potency (IC_{50}) was defined as the concentration of the drug required to produce 50% inhibition of the agonist-stimulated functional response. Data derived from the cytokine assays were calculated as mean and standard error (SEM) values which represent the variability among identically treated culture wells. The dose-dependent effect of pharmacological agents and IC_{50} 's were determined by linear regression. Data are expressed as mean \pm S.E.M. from 3 - 5 independent experiments.

D. Results.

Exposure of HCE to 30 μ M of histamine increased IL-6 and IL-8 secretion 1.59 ± 0.19 and 1.80 ± 0.28 fold above basal levels, respectively. (Basal levels of the cytokines were 153 ± 42 pg/ml, $n = 4$, for IL-6 and 197 ± 48 pg/ml, $n = 6$, for IL-8.)

Treatment of HCE with drugs possessing anti-histaminic activity and available for topical ocular administration prior to histamine exposure resulted in concentration-dependent inhibition of IL-6 secretion and IL-8 secretion. The results are shown below in Table 1.

The potency of emedastine in intact cells is consistent with its activity determined in receptor binding assays using tissue homogenates. Levocabastine also inhibited the IL-6, and IL-8 secretion at a level consistent with its H_1 -receptor binding affinity. Antazoline and pheniramine, two first generation topical ocular anti-histamine compounds, were dramatically less potent inhibitors of IL-6 and IL-8 secretion than predicted from their histamine H_1 -receptor binding affinities (20 – 140-fold). Olopatadine, however, was more potent than predicted from its published histamine H_1 -receptor binding affinity (36 nM). Olopatadine, antazoline and pheniramine exhibit similar H_1 binding affinities (32 – 39 nM). Yet, olopatadine was approximately 10-fold more potent as an inhibitor of cytokine secretion (IC_{50} 's of 5.5 nM and 1.7 nM for IL-6 and IL-8 secretion, respectively) than predicted from binding data. These results indicate that, unlike the other compounds tested, olopatadine's

ability to inhibit cytokine secretion is attributable to something more than H₁-receptor binding affinity.

Table 1: Histamine H₁ Antagonists: Inhibition of IL-6 and IL-8 Secretion in Human Conjunctival Epithelial Cells and H₁ Receptor Binding Affinities

H ₁ Antagonist	IL-6	IL-8	H ₁ Binding
	IC ₅₀ (nM)	IC ₅₀ (nM)	K _i (nM)
Emedastine ^a	2.5	4.0	1.22 *
Olopatadine ^b	5.5	1.7	36.0 §
Levocabastine ^c	25.1	11.9	52.6 *
Antazoline ^d	1014	652	38.4 *
Pheniramine ^e	4826	1216	33.9 *

^a 1H-Benzimidazole, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl), (E)-2-butenedioate (1:2).

^b Z-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.

^c (-)-trans-1-[cis-4-Cyano-4-(p-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid monohydrochloride.

^d 4,5-Dihydro-N-phenyl-N-(phenylmethyl)-1H-imidazole-2-methanamine.

^e N,N-Dimethyl-γ-phenyl-2-pyridine-propanamine.

* Sharif et al., *J Ocul Pharmacol.*, 10:653-664 (1994)

§ Yanni et al., *Ann Allergy Asthma Immunol.*, 79:541-545 (1997)

WHAT IS CLAIMED IS:

1. A method of treating or preventing ocular neovascularization and non-allergic ophthalmic inflammatory disorders involving cytokine release from human ocular cells comprising the step of administering to the eye a composition comprising a therapeutically-effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof.
2. The method of Claim 1 wherein the composition is a topically administrable solution and the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 w/v.% to about 5% (w/v).
3. The method of Claim 2 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 0.001% (w/v).
4. The method of Claim 3 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.0005% (w/v).
5. The method of Claim 1 wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, substantially free of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.
6. The method of Claim 5 wherein the composition is a topically administrable solution and the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

7. The method of Claim 6 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 0.001% (w/v).

5

8. The method of Claim 7 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is 0.0005% (w/v).

10

9. The method of Claim 1 wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, substantially free of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.

15

10. The method of Claim 9 wherein the composition is a topically administrable composition and the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

20

11. The method of Claim 10 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 0.001% (w/v).

25

12. The method of Claim 11 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.0005% (w/v).

30

13. The method of Claim 1 wherein the non-allergic ophthalmic inflammatory disorder is selected from the group consisting of dry eye, keratitis, blepharitis, uveitis and inflammation related to infection.

14. The method of Claim 1 wherein the ocular neovascularization and non-allergic ophthalmic inflammatory disorders involve cytokine release from human conjunctival epithelial cells.

INTERNATIONAL SEARCH REPORT

Inter: nal Application No

PCT/US 99/13275

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
------------	--	-----------------------

P, X	<p>CUTARELLI, P.E. ET AL.: "The painful eye. External and Anterior Segment Causes" CLINICS IN GERIATRIC MEDICINE, vol. 15, no. 1, February 1999 (1999-02), pages 103-112, XP002119437 page 105, paragraph 3 -page 106, paragraph 1 page 106, line 15</p> <p style="text-align: center;">--- -/--</p>	1-14
------	--	------

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 October 1999

Date of mailing of the international search report

03/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Economou, D

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 99/13275

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>YANNI, J.M. ET AL.: "Inhibition of Histamine-Induced Human Conjunctival Epithelial Cell Responses by Ocular Allergy Drugs"</p> <p>ARCH.OPHTHALM.,</p> <p>vol. 117, no. 5, May 1999 (1999-05), pages 643-647, XP002119438</p> <p>usa</p> <p>abstract</p> <p>page 646, right-hand column, last line</p> <p>-page 647, left-hand column, paragraph 1</p> <p>page 647, left-hand column, last paragraph</p> <p>-----</p>	1-14